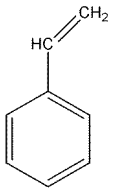
Styrene
CAS No. 100-42-5
Reasonably anticipated to be a human carcinogen
First listed in the *12th Report on Carcinogens*



Carcinogenicity
Styrene is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity in humans, sufficient evidence of carcinogenicity in experimental animals, and supporting mechanistic data.

Human Studies
There is limited evidence of the carcinogenicity of styrene in humans based on studies of workers exposed to styrene showing (1) increased mortality or incidence of lymphohematopoietic cancer and (2) increased levels of DNA adducts and genetic damage in lymphocytes from exposed workers. Elevated risks of cancer were found among workers with higher exposure to styrene after an appropriate latency period. In some studies, the risks increased with increasing measures of exposure, such as average exposure, cumulative exposure, or number of years since first exposure. However, the types of lymphohematopoietic cancers observed in excess varied somewhat across different cohort studies, and excess risks were not always found in smaller cohorts. Causality is not established, as the possibility of confounding from other chemical exposures or chance cannot be completely ruled out; however, a causal relationship between styrene exposures and cancer in humans is credible and supported by the finding of DNA adducts and chromosomal aberrations in lymphocytes from styrene-exposed workers.

Most of the evidence in humans comes from occupational cohort studies in three major industries: (1) the reinforced plastics industry, (2) the styrene-butadiene rubber industry, and (3) the styrene monomer and polymer industry. The most informative studies for evaluating the carcinogenicity in humans are of workers in the reinforced plastics industry and the styrene-butadiene synthetic rubber industry. Workers in the reinforced plastics industry were exposed to the highest levels of styrene, and they had few other potentially carcinogenic exposures. However, the majority of the workers had short periods of employment. In the styrene-butadiene rubber industry, workers were exposed to lower levels of styrene than in the reinforced plastics industry, but a large number of workers studied had adequate follow-up to permit detailed analyses of lymphohematopoietic cancers. The principal limitation of the latter studies is potential confounding due to other exposures, principally butadiene, which is a known human carcinogen associated with leukemia risk (Grosse *et al*. 2007, NTP 2004).

The two cohort studies with the largest number of person-years, an incidence study of male Danish workers (Kolstad *et al.* 1995, Kolstad *et al.* 1994) and a European multinational mortality study of male and female workers (which included a subset of the Danish workers) (Kogevinas *et al.* 1994) were considered to be the most informative studies in the reinforced plastics industries. In the styrene-butadiene industry, the major study was the large multi-plant cohort mortality study of male and female styrene-butadiene workers in the United States and Canada by Delzell and colleagues (Delzell *et al.* 2006, Graff *et al.* 2005), which encompassed most of the workers from two earlier cohorts (a smaller study reported by Meinhardt *et al.* 1978, and a larger study reported by Matanoski *et al.* 1990). In both industries, the studies conducted internal analyses (i.e., used unexposed members of the cohort as the comparison group); such analyses are less susceptible to confounding than those using external referent populations. Internal analyses were used to evaluate exposure-response relationships for cumulative exposure, average exposure, peak exposure (a measure of exposure intensity), or time since first exposure in the multinational cohort study of reinforced plastics workers (Kogevinas *et al.* 1994) and in the multi-plant study of styrene-butadiene workers (Delzell *et al.* 2006). Without *a priori* knowledge, it is difficult to know which exposure metric is most appropriate for evaluating causality, so a positive relationship observed with any exposure metric is a concern. The studies also conducted standardized mortality ratio (SMR) or standardized incidence ratio (SIR) analyses, which compared observed with expected events (deaths or incident cases) based on national mortality or incidence rates.

Lymphohematopoietic cancer

Increased risks for lymphohematopoietic cancers (leukemia or lymphoma or all) were found among styrene-exposed workers in both the reinforced plastics and styrene-butadiene rubber industries. The evidence primarily comes from positive exposure-response relationships found in the multinational European study (reinforced plastics workers) (Kogevinas *et al.* 1994) and the multi-plant cohort study of styrene-butadiene workers (Delzell *et al.* 2006), and is supported by the findings of increased cancer risks among subgroups of workers with higher exposure to styrene or longer latency (Kolstad *et al.* 1994, Delzell *et al.* 2006). Although co-exposure to butadiene is a concern in the styrene-butadiene industry, the finding of increased cancer risk in the reinforced plastics industry, where such confounding is not an issue, suggests that styrene is a potential risk factor for lymphohematopoietic cancers.

Reinforced Plastic Industry: Positive (significant or approaching significant) exposure-response relationships were found for average exposure and time since first hire for all lymphohematopoietic cancers (P_{trend} = 0.019 and P_{trend} = 0.012, respectively) and malignant lymphoma (P_{trend} = 0.052 and P_{trend} = 0.072, respectively) in the multinational cohort (Kogevinas *et al.* 1994). No relationship with cumulative exposure was observed; however, analyses of cumulative exposure are limited by the control for duration of exposure, which is correlated with cumulative exposure and thus may represent over-control. Moreover, measures of intensity of exposure (such as average exposure) may be more informative for evaluating risks in populations with a high-percentage of short-term workers than cumulative exposure. Among Danish reinforced plastics workers,

significant increases in leukemia incidence were observed among workers with earlier dates of first exposure (1964 to 1970, during which time the highest exposure levels occurred) and 10 or more years of latency (Kolstad *et al.* 1994). Higher risks were also found among workers with shorter duration of exposure (< 1 year) than longer duration of exposure. However, estimates of duration of employment did not agree with a secondary employment assessment, which suggested that many of those classified as short-term workers were long-term workers. Similar findings for leukemia were found in the internal analyses using unexposed workers as controls for short-term workers, thus helping rule out confounding by socioeconomic status and lifestyle factors of the short-term workers.

Styrene-butadiene Industry: Significantly increased risks (SMRs) for NHL, NHL-chronic lymphocytic leukemia (CLL) and leukemia (overall and specific types) were found among subgroups of workers with long durations of employment and long latency (greater than 10 years of employment and 20 to 29 years or 30+ years latency), in specific job groups, and with the highest levels of cumulative exposure to styrene (Delzell *et al.* 2006, Graff *et al.* 2005, Sathiakumar *et al.* 2005). In an attempt to disentangle the effects of styrene from butadiene, internal analyses were conducted for quartiles of cumulative exposure or exposure to periodic spikes of high styrene concentrations (styrene peaks, defined as ≥ 50 ppm) involving statistical models with (1) styrene only, (2) styrene and butadiene, and (3) styrene, butadiene, and skin exposure to dimethyldithiocarbamate (DMDTC). The numbers of cases in each exposure level were small, which limited the power to detect statistically significant risk estimates. No trend analyses were reported.

These analyses suggested an exposure-response relationship between NHL or NHL-CLL and exposure to styrene that was not explained by exposure to butadiene. Relative risks of NHL or NHL-CLL (combined) increased with increasing levels of cumulative exposures to styrene and were not attenuated after controlling for exposure to butadiene. However, the relative risks were only statistically significant for the highest exposure level of styrene in the styrene only model. Exposure to butadiene was not associated with NHL-CLL or NHL risk in this study (Delzell *et al.* 2006, Graff *et al.* 2005). The strongest evidence for an association between styrene exposure and leukemia comes from analyses of cancers among workers exposed to styrene peaks. Relative risks increased with exposure to increasing numbers of styrene peaks in all three chemical models and statistically significant risk estimates were observed at the two highest exposure levels after controlling for butadiene exposure. Analysis by cumulative exposure showed increased relative risks of leukemia with increasing cumulative styrene exposure, but the response was attenuated with control for butadiene exposure, and no association remained after additional control for DMDTC. (The relevance of including DMDTC in these models is not clear, since there is no current evidence that DMDTC is carcinogenic in animals or humans.)

Significantly increased risks for lymphomas (ICD codes 200 & 202, which are the same ICD codes for NHL) and all lymphohematopoietic cancers and exposure to styrene (1-

ppm time-weighted average) were also found in a nested case-control study from the Matanoski cohort in a statistical model that accounted for exposure to butadiene. Although the study population overlaps with the Delzell study, it provides supporting evidence for the increased cancer risks for lymphoma reported in the Delzell study since the case-control study used a different exposure assessment (based on measurements) and a different statistical model (Matanoski *et al.* 1997).

Other tumors: Some studies in the reinforced plastics industry provide suggestive evidence for increased incidences or mortality due to pancreatic and esophageal tumors; however, no excess of cancer at these sites was observed in the styrene-butadiene industry (NTP 2008). Increases in cancer at these sites were also observed in some of the individual cohort studies (Ruder *et al*. 2004, Wong *et al.* 1994, Kolstad *et al.* 1995), and there was some evidence of an exposure-response relationship with pancreatic cancer (NTP 2008). The risk of pancreatic cancer was somewhat higher among the Danish workers with longer-term employment and earlier start date in the internal analyses (Kolstad *et al.* 1995), and increased with cumulative exposure in the European multi-plant cohort (P_{trend} = 0.068) (Kogevinas *et al.* 1994, 1993).

Genetic damage: DNA adducts (primarily, N^2-guanine and O^6-guanine, but also ßN1-adenine adducts) were reported in circulating white blood cells in studies of styrene-exposed workers employed mainly in the reinforced plastic plants. In most studies in workers, single-strand DNA breaks showed exposure-related increases. A meta-analysis of 22 studies found a positive association (weighted frequency ratio = 2.18, 95% CI = 1.52 to 3.13) between styrene exposure level and chromosomal aberration frequency when exposure levels were dichotomized as greater than or less than a threshold value of 30 ppm for an 8-hour time-weighted average (Bonassi *et al.* 1996, NTP 2008).

Experimental Animal Studies

There is sufficient evidence for the carcinogenicity of styrene in experimental animals based on the induction of tumors in multiple studies in mice exposed to styrene by two routes of exposure. The most robust studies are a two-year inhalation study in CD-1 mice (Cruzan *et al.* 1998) and a two-year oral gavage study in $B6C3F_1$ mice (NCI 1979). Significantly increased incidences of alveolar/bronchiolar adenoma (benign lung tumor) and alveolar/bronchiolar adenoma or carcinoma (combined) occurred in male and female CD-1 mice; significantly increased incidences of alveolar/bronchiolar carcinoma were also observed in female CD-1 mice. In male $B6C3F_1$ mice, exposure to styrene was associated with a significantly increased incidence of alveolar/bronchiolar adenoma and carcinoma (combined), and a significant positive dose-response trend was observed (NCI 1979, NTP 2008). No tumors were observed in the concurrent control animals dosed only with the vehicle used to deliver styrene, corn oil. The incidence of tumors in the concurrent vehicle control animals was compared with results from historical controls [lung tumor incidence was 4% (11/273)] treated with corn oil and from the same time period (prior to 1979), with similar study duration, and from the same supplier as used in the NCI study. This comparison indicated that the incidence in the concurrent vehicle controls in the NCI study was not unusually low, and supports the

finding that the increased incidence of lung tumors was exposure-related (NTP 2008). These findings are supported by findings of lung tumors in both sexes of O20 mice exposed to styrene (Ponomarkov and Tomatis 1978). In this study, a single dose of styrene was administered to pregnant dams on gestational day 17, and pups were dosed orally once a week for 16 weeks after weaning. A significantly higher incidence and earlier onset of lung tumors (adenoma and carcinoma combined) occurred in both male and female O20 mice compared with vehicle controls as early as 16 weeks after weaning. No significant increases in tumor incidence compared with controls were observed in a similar study in C57Bl mice administered a much lower dose of styrene.

Data from experimental cancer studies with rats are insufficient for reaching a conclusion.

Other Relevant Data

Styrene can be absorbed and widely distributed throughout the body through inhalation, ingestion, or skin contact, but the most important route of exposure in humans in occupational settings is by inhalation (IARC 2002). Metabolic activation of styrene results in formation primarily of the genotoxic metabolite styrene-7,8-oxide, which can be detoxified by glutathione conjugation or conversion to styrene glycol by microsomal epoxide hydrolase. Further oxidation of styrene glycol produces mandelic acid and phenylglyoxylic acid, the major metabolites identified in the urine of styrene-exposed workers (Manini *et al.* 2002). Systemic distribution of styrene-7,8-oxide in workers has been demonstrated from measurements of styrene-7,8-oxide-based hemoglobin adducts in erythrocytes and DNA adducts in lymphocytes (Tornero-Valez *et al.* 2001, Vodicka *et al*. 2003, NTP 2008).

Styrene is metabolized primarily in the liver and the lung. The Clara cell is regarded as the major cell type in the lung that activates styrene to styrene-7,8-oxide following inhalation exposure. The initial step in styrene metabolism is catalyzed by cytochromes P450; CYP2E1 and CYP2F (2F1 in humans, 2f2 in mice, and 2F4 in rats) are the predominant enzymes in humans and experimental animals. In animals, CYP2E1 predominates in the liver, while Cyp2f2 is the primary enzyme in mouse lung. CYP2A13, CYP2F1, CYP2S1, CYP3A5, and CYP4B1 are preferentially expressed in the lung compared with the liver in humans, and the human CYP2F1 has been shown to be capable of metabolizing styrene when expressed *in vitro* (Nakajima *et al.* 1994, NTP 2008). Because styrene-7,8-oxide contains a chiral carbon, this and some subsequent styrene metabolites can exist as either *R*- or *S*-enantiomers. A second and minor pathway of styrene metabolism involves oxidation of the aromatic ring, resulting ultimately in formation of 4-vinylphenol, which has been detected in humans (Manini *et al.* 2003, Pfäffli *et al.* 1981) and rats (Bakke and Scheline 1970), and is implicated to occur in mice *in vivo* through indirect measures (Boogaard *et al.* 2000*)*.

The primary metabolite of styrene, styrene-7,8-oxide, is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* based on sufficient evidence in experimental animals. Styrene-7,8-oxide induced increased incidences of

forestomach tumors in rats and mice and liver tumors in male mice after oral administration (NTP 2004).

The mechanisms of styrene carcinogenicity are not fully known. The proposed mechanisms for the carcinogenicity of styrene include both genotoxic and epigenetic pathways. These mechanisms, which are not necessarily mutually exclusive, include: (1) metabolic conversion of styrene to styrene-7,8-oxide and subsequent induction of DNA damage in the target tissue and (2) cytotoxic effects of styrene metabolites including styrene-7,8-oxide and 4-vinylphenol in the mouse lung, resulting in cellular proliferation, pulmonary hyperplasia, and tumor formation (Cohen *et al.* 2002, NTP 2008, Cruzan *et al.* 2002).

The majority of genotoxic effects (DNA damaging) associated with styrene exposure are thought to be due to styrene-7,8-oxide. The predominant DNA adducts formed from styrene-7,8-oxide exposure are at the N7, N^2, and O^6 positions of guanine (which have been detected in cells*)*; however, styrene-7,8-oxide adducts can also form at the N1, N3, and N^6 positions of adenine, the N3, N^4, and O^2 positions of cytosine, and the N3 position of thymine. N7-adducts are formed in the greatest amount but are the least persistent (that is they are either repaired or lost), while O^6-adducts are formed in the least amount but are the most persistent. Other than the N7-guanine and N3-adenine adducts, the styrene-7,8-oxide-DNA adducts listed above are considered promutagenic, because they can interfere with base-pairing and lead to miscoding during DNA replication. The major styrene-7,8-oxide adduct at N7-guanine may also be promutagenic, because it can undergo spontaneous or glycosylase-mediated depurination, thus creating abasic sites that promote coding errors during DNA replication (reviewed by Vodicka *et al.* 2006). Styrene-7,8-oxide, without metabolic activation, is mutagenic in most *in vitro* systems, leading to a variety of transition and transversion mutations (Bastolová and Podlutsky 1996). Both styrene and styrene-7,8-oxide caused cytogenetic effects (sister chromatid exchange, chromosomal aberrations, and micronuclei) in human lymphocytes or other mammalian cells *in vitro* (NTP 2008). In animals exposed to styrene, DNA adducts (N7-guanine, O^6-guanine, N1-adenine) have been detected in liver and lung cells of mice and rats exposed to styrene *in vivo* (NTP 2008). Most animal studies have also demonstrated single-strand DNA breaks from styrene-7,8-oxide or styrene exposure (Walles and Orsen 1983, Vaghef and Hellman 1998, Vodicka *et al*. 2001), and the most consistent cytogenetic effect reported has been the induction of sister chromatid exchange (NTP 2008).

Styrene-7,8-oxide has been measured in the blood of styrene-exposed workers, and several different styrene-7,8-oxide-based DNA adducts have been measured in lymphocytes of workers. Styrene-7,8-oxide-DNA adducts identified in exposed workers include O^6-guanine, N1-adenine, and N^2-guanine. Adduct studies in workers show that a DNA-reactive intermediate of styrene metabolism circulates in the blood of styrene-exposed humans (NTP 2008). The most consistent cytogenetic effects in styrene-exposed workers are single-strand DNA breaks and induction of chromosomal aberrations (Bonassi *et al.* 1996, Cohen *et al.* 2002, NTP 2008).

Styrene induces lung tumors and pulmonary toxicity in mice but does not cause lung tumors in rats (Cruzan *et al*. 1998, 2001). Several studies have not found evidence of toxicity in the lungs of rats exposed to styrene (Cruzan *et al.* 1997, 1998, Gamer *et al.* 2004, Green *et al*. 2001), although one study reported toxicity to bronchiolar and alveolar type II cells in Sprague-Dawley rats exposed to styrene by either i.p. injection or inhalation (Coccini *et al.* 1997). Alveolar/bronchiolar hyperplasia from styrene exposure has been hypothesized to play a role in the development of lung tumors in mice. Effects of repeated styrene exposure included focal crowding of bronchiolar cells, bronchiolar epithelial hyperplasia, and bronchiolar-alveolar hyperplasia (Cruzan *et al.* 2001). Interspecies differences in lung toxicity are proposed to result from differences in the extent of metabolism of styrene to ring-oxidized metabolites by CYP2F in the Clara cells of the lung (Cruzan *et al.* 2002). Indirect data supporting the role of CYP2F in styrene-induced lung toxicity comes from short-term i.p. injection studies with wild-type and CYP2E1 knock-out mice, which showed similar lung toxicity (Carlson 2004). Also, the cytotoxic effects of styrene and tumor formation were seen primarily in respiratory tissues that are high in CYP2F isoforms, and CYP2F inhibitors prevented cytotoxicity (Cruzan *et al.* 2002). Styrene-7,8-oxide, 4-vinylphenol, and 4-vinylphenol metabolites can be formed by Cyp2f2. Metabolites formed from ring oxidation, which include 4-vinylphenol, are several-fold higher in mice compared with rats (Boogaard *et al.* 2000, Cruzan *et al.* 2002). Furthermore, some data suggest that 4-vinylphenol is more toxic than styrene-7,8-oxide in mouse lung, but the two molecules were tested in separate experiments in two different strains of mice (Carlson *et al*. 2002, Gadberry *et al.* 1996). Short-term toxicity studies of 4-vinylphenol in wild-type and CYP2E1 knock-out mice and studies with CYP inhibitors suggest that metabolites of 4-vinylphenol are responsible for its lung and liver toxicity in mice (Carlson 2002, Vogie *et al*. 2004). However, the Cyp2f2-mediated cytotoxicity hypothesis has not yet been tested in long-term cancer assays in mouse models lacking the Cyp2f2 gene.

The induction of lung tumors in mice, but not in rats, has also been observed in exposure studies in experimental animals of epoxides and other epoxide-forming chemicals, including the *known human carcinogens* vinyl chloride, 1,3-butadiene, and ethylene oxide (NTP 2004, 2008). Further, although quantitative differences in styrene disposition exist across species, there are no demonstrated qualitative differences between humans and laboratory animals that contradict the relevance of the rodent cancer studies for evaluations of human hazard. The detection of styrene-7,8-oxide-DNA adducts at base-pairing sites and chromosomal aberrations in lymphocytes of styrene-exposed workers supports the potential human cancer hazard from styrene through a genotoxic mode-of-action.

Properties

Styrene is an aromatic hydrocarbon that occurs as a colorless or yellowish, viscous liquid with a sweet, floral odor (HSDB 2008). It has a flash point of 34°C (closed cup), lower explosive limit of 0.9% to 1.1% (v/v), upper explosive limit of 6.1% to 6.8% (v/v), and an autoignition temperature of 490°C. Styrene is highly flammable and easily ignited by heat, sparks, or flames and its vapors may form explosive mixtures with air due to the formation of peroxides. Styrene may polymerize when contaminated by oxidizing agents or halides, or when heated, and it emits acrid fumes upon decomposition (NSC 2004, SPA 2008). Usually styrene is stabilized for safe storage, transport, and use by an inhibitor, commonly *p*-tert-butylcatechol (HSDB 2008). Other typical impurities are ethylbenzene, polymer content, aldehydes, peroxides (as H_2O_2), benzene, sulfur, and chlorides. The physical and chemical properties of styrene are summarized in the following table.

Property	Information
Molecular weight	104.2
Specific gravity	0.906 at 20°C
Melting point	–31
Boiling point	145°C
Octanol-water partition coefficient (log K_{ow})	2.95
Water solubility	310 mg/L at 25°C
Vapor pressure (mm Hg)	6.4 at 25°C
Vapor density	3.6 (air = 1)

Sources: HSDB 2008, IARC 1994.

Use

Styrene is an important industrial chemical used in the synthesis and manufacture of polystyrene and hundreds of different copolymers, as well as numerous other industrial resins (Guest 1997). Styrene producers sell styrene monomer to companies that use the styrene to make various compounds and resins. Fabricators then process the resins into a wide variety of products (Cohen *et al.* 2002). Roughly 99% of the industrial resins produced from styrene can be grouped into six major categories: polystyrene (50%), styrene-butadiene rubber (15%), unsaturated polyester resins (glass reinforced) (12%), styrene-butadiene latexes (11%), acrylonitrile-butadiene-styrene (10%), and styrene-acrylonitrile (1%). Another minor category of use is unsaturated polyester resins (not reinforced) (Luderer *et al.* 2005).

Polystyrene is used extensively in the manufacture of plastic packaging, thermal insulation in building construction and refrigeration equipment, and disposable cups and containers. Styrene polymers and copolymers also are increasingly used to produce

various housewares, food containers, toys, electrical devices, automobile body parts, corrosion-resistant tanks and pipes, various construction items, carpet backings, house paints, computer printer cartridges, insulation products, wood floor waxes and polishes, adhesives, putties, personal care products, and other items, and they are used in paper processing (IARC 2002, Luderer *et al.* 2005, NLM 2008).

Styrene-butadiene rubber is the most widely used synthetic rubber in the world. (ICIS 2008). Over 70% of styrene-butadiene rubber is consumed in the manufacture of tires and tire products; however, non-tire uses are growing, with applications including conveyor belts, gaskets, hoses, floor tiles, footwear, and adhesives.

Another major use of styrene is as a cross-linking agent in polyester resins used in gel-coating and laminating operations in the production of glass fiber–reinforced plastic products such as boats, bathtubs, shower stalls, tanks, and drums (EPA 1997, Miller *et al.* 1994). The resins generally contain between 30% and 50% styrene by weight (EPA 1997).

Production

There are two commercially viable methods to produce styrene (ATSDR 1992, HSDB 2008). The most common process, which accounts for over 90% of the total world styrene production, involves catalytic dehydrogenation of ethylbenzene. The second process involves oxidation of ethylbenzene to its peroxide, which is then reacted with propylene to produce propylene oxide and alpha-methylphenyl carbinol. The carbinol is then dehydrated to produce styrene.

U.S. production of styrene has risen fairly steadily since 1960. Berthiaume and Ring (2006) estimated U.S. styrene production to be 11,387 million pounds in 2006. Between 1960 and 2006, the maximum estimated production level was 11,897 million pounds in 2000, and the minimum was 1,740 million pounds in 1960. As of 2006 eight active producers of styrene were identified in the United States (Berthiaume and Ring 2006). The three largest of these producers accounted for 54% of domestic production in 2006. U.S. consumption of styrene in 2006 was 9,600 million pounds with over 99% consumed in the production of polymers and copolymers.

Berthiaume and Ring (2006) and USITC (USITC 2008a, 2008b) each reported a steadily increasing trend in both imports and exports from 1975 through 2007. The minimum level for imports was 7 million pounds in both 1975 and 1977, and the maximum level was 1,475 million pounds in 2007. The minimum level for exports was 574 million pounds in 1975, and the maximum level was 4,200 million pounds in 2007.

Exposure

Exposure to styrene can occur in both occupational and non-occupational settings. Workers in certain occupations are potentially exposed to much higher levels of styrene than the general public. In occupational settings, workers can be exposed during production processes for styrene monomer, polystyrene and various styrene copolymers, glass fiber–reinforced plastics, and styrene-butadiene rubber; exposure also can occur in other miscellaneous occupations (ATSDR 1992, IARC 2002).

The highest occupational exposure levels to styrene occur in the fabrication of objects such as boats, car and truck parts, tanks, tubs, and shower stalls from glass fiber–reinforced polyester composite plastics (IARC 2002). Historically, the highest styrene exposure levels for reinforced-plastics workers were in the range of several hundred parts per million, although declining levels (estimated 10-fold decrease) have been reported to have occurred over the past several decades due to improved work practices and products (Kolstad *et al.* 2005). In general, average exposure levels reported since the 1980s have been at levels less than 100 ppm. In 2006, the U.S. Bureau of Labor Statistics estimated that 32,510 workers were employed as "Fiberglass Laminators and Fabricators" (defined as "laminate layers of fiberglass on molds to form boat decks and hulls, bodies for golf carts, automobiles, or other products"). "Ship and boat building" was the largest subcategory in this Standard Occupational Classification segment, with 12,910 employees (BLS 2007).

Generally lower levels are seen in the styrene-butadiene rubber and the styrene monomer and polymer industries than the glass fiber–reinforced-plastics industry, although significant exposures to workers can still occur. Mean levels for these industries generally have been reported to be less than 20 ppm. No data were found for the number of employees in these industries.

Low levels of styrene (usually in the low ppb range) have been reported in a variety of occupational settings, including nuclear power plants, photocopy centers, a petrochemical complex, printing plants, wood surface coating operations, tollbooths, a waste incinerator, and during the production of PVC film (NTP 2008). IARC (2002) reported levels in the low ppm range in a sculpture class where polyester resins were used, during the production of buttons, and during firefighting. Higher levels were seen during the production or use of paints and putties (exceeding 20 ppm), for taxidermists (up to 70 ppm), and during the manufacture of cooking ware (up to 186 ppm).

Styrene exposure to the general public can occur through environmental contamination. Styrene has been measured in outdoor air but generally higher levels have been found in indoor air, drinking water, groundwater, surface water, soil, and food. Styrene can be emitted to the air from industrial production and use of styrene and styrene-based polymers and copolymers, motor vehicle emissions and other combustion processes, off-gassing of building materials and consumer products, and cigarette smoking (ATSDR 1992, IARC 1994). Numerous spills containing styrene have been reported to the National Response Center (NRC 2008) since 1990, and these spills have the potential to contaminate air, water, soil, and food supplies.

Studies have shown that food can be a major contributor to styrene exposure for the general population (Cohen *et al.* 2002, Holmes *et al.* 2005, Lickly *et al.* 1995b, Tang *et al.* 2000). Styrene has been detected as a constituent of a wide range of foods and beverages, with the highest measured levels occurring in unprocessed, raw cinnamon, possibly resulting from the natural degradation of cinnamic acid derivatives (IARC 1994). Styrene is also known to occur at very low concentrations in many agricultural foods, although it is not known whether the styrene is produced endogenously or results from environmental contamination (Tang *et al.* 2000). The presence of styrene in

packaged foods is reported to be due primarily to monomer leaching from polystyrene containers (ATSDR 1992, Howard 1989). The primary factors that determine the rate of migration of styrene monomer from polystyrene containers include the lipophilicity of the food, surface area of the container per volume of food, duration of contact, and food temperature (ATSDR 1992, Choi *et al.* 2005, EU 2002, Lickly *et al.* 1995a). Uptake of styrene by biological organisms is expected to be low (EU 2002, Howard 1989, HSDB 2008); however, styrene has been detected in fish and other aquatic organisms.

Several authors have estimated exposure levels to styrene from various media for the general public of the United States and other countries. Fishbein (1992) estimated the relative significance of different routes of exposure to styrene showing the importance of polluted urban environments and indoor air levels. Smoking cigarettes also contributed levels similar to those for indoor air and polluted outdoor air. Health Canada (1993) estimated daily styrene intakes from various media for different age groups of the Canadian general population and reported daily intakes from sources other than smoking of less than 0.8 μg/kg body weight (b.w.) per day for children and less than 0.4 μg/kg b.w. for adults, but intakes by cigarette smokers were as high as 3.5 μg/kg b.w. per day. While this study demonstrated that inhalation of both indoor and outdoor air and ingestion of food are important sources of exposure for non-smokers, the study also showed that exposure from smoking cigarettes was roughly 10 times that from all other routes (indoor and outdoor air, drinking water, soil, and food) combined. Cohen *et al.* 2002 estimated styrene exposure to be six times higher for smokers than for non-smokers. Miller *et al.* (1998) reported that up to 15% of non-smokers' styrene exposure could be attributed to environmental tobacco smoke.

Several studies have confirmed styrene exposure to the general public through the use of biological monitoring. Styrene was detected in all eight human breast milk samples from women in four U.S. cities and in 100% of wet adipose tissue samples [number of samples not reported] in a U.S. EPA study in 1982 (Howard 1989). Styrene also has been detected in the general population in blood at a mean concentration of 0.4 μg/L and in exhaled breath at mean concentrations of 0.7 to 1.6 $\mu g/m^3$ (ATSDR 1992). A mean styrene blood level of 0.07 μg/L was calculated based on more than 600 blood samples of U.S. residents assessed in the Centers for Disease Control and Prevention's Third National Health and Nutrition Examination Survey (NHANES III) (Ashley *et al.* 1994).

Regulations

Department of Homeland Security

46 CFR 150 and 151 detail procedures for shipping styrene monomer and for shipping styrene monomer and various styrene co-polymers with incompatible mixtures

Department of Transportation (DOT)

Considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material

Environmental Protection Agency (EPA)

Clean Air Act

NESHAP: Listed as a hazardous air pollutant

NSPS: Synthetic Organic Chemical Manufacturing Industry (SOCMI) facilities that meet the definition of a new source and produce styrene are subject to provisions for the control of VOC emissions

Control of Emissions of Hazardous Air Pollutants from Mobile Sources: Listed as a mobile source air toxic

Clean Water Act

Styrene has been designated a hazardous substance with a reportable quantity (RQ) of 1,000 lb

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.1 mg/L

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.1 mg/L

The food additive poly (2-vinylpyridine-co-styrene) may be safely used as nutrient protectant in feed for beef cattle and dairy cattle and replacement dairy heifers with residual styrene levels not to exceed 200 ppb

Polystyrene basic polymers used as components of articles intended for use in contact with food shall contain not more than 1 weight percent of total residual styrene monomer (0.5 weight percent on certain fatty foods)

Rubber-modified polystyrene basic polymers used as components of articles intended for use in contact with food shall contain not more than 0.5 weight percent of total residual styrene monomer

Styrene-maleic anhydride co-polymers may be used as articles or as components of articles intended for use in contact with food provided that conditions detailed in the regulation are met, including a maximum residual styrene monomer of 0.3% by weight

Styrene-acrylic co-polymers may be used as components of the food-contact surface of paper and paperboard provided that certain conditions are met, including residual styrene monomer levels in the polymer not exceeding 0.1% by weight

Occupational Safety and Health Administration (OSHA)

Acceptable peak exposure = 600 ppm (5-minute maximum peak in any 3 hours)

Ceiling concentration = 200 ppm

Permissible exposure limit (PEL) = 100 ppm

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – short-term exposure limit (TLV-STEL) = 40 ppm

Threshold limit value – time-weighted average limit (TLV-TWA) = 20 ppm

Biological exposure indices:

Mandelic acid plus phenylglyoxylic acid in urine, end of shift = 400 mg/g creatinine

Styrene in venous blood, end of shift = 0.2 mg/L

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health limit (IDLH) = 700 ppm

Short-term exposure limit (STEL) = 100 ppm

Recommended exposure limit (REL) = 50 ppm

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